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# Personalized mechanical ventilation in acute respiratory distress syndrome

Paolo Pelosi[1,2*], Lorenzo Ball[1,2], Carmen S. V. Barbas[3,4], Rinaldo Bellomo[5,6,7,8,9], Karen E. A. Burns[10,11], Sharon Einav[12], Luciano Gattinoni[13], John G. Laffey[14], John J. Marini[15], Sheila N. Myatra[16], Marcus J. Schultz[17,20,21], Jean Louis Teboul[18] and Patricia R. M. Rocco[19]

## Abstract

A personalized mechanical ventilation approach for patients with adult respiratory distress syndrome (ARDS) based on lung physiology and morphology, ARDS etiology, lung imaging, and biological phenotypes may improve ventilation practice and outcome. However, additional research is warranted before personalized mechanical ventilation strategies can be applied at the bedside. Ventilatory parameters should be titrated based on close monitoring of targeted physiologic variables and individualized goals. Although low tidal volume ($V_T$) is a standard of care, further individualization of $V_T$ may necessitate the evaluation of lung volume reserve (e.g., inspiratory capacity). Low driving pressures provide a target for clinicians to adjust $V_T$ and possibly to optimize positive end-expiratory pressure (PEEP), while maintaining plateau pressures below safety thresholds. Esophageal pressure monitoring allows estimation of transpulmonary pressure, but its use requires technical skill and correct physiologic interpretation for clinical application at the bedside. Mechanical power considers ventilatory parameters as a whole in the optimization of ventilation setting, but further studies are necessary to assess its clinical relevance. The identification of recruitability in patients with ARDS is essential to titrate and individualize PEEP. To define gas-exchange targets for individual patients, clinicians should consider issues related to oxygen transport and dead space. In this review, we discuss the rationale for personalized approaches to mechanical ventilation for patients with ARDS, the role of lung imaging, phenotype identification, physiologically based individualized approaches to ventilation, and a future research agenda.

**Keywords:** Tidal volume, Driving pressure, Transpulmonary pressure, Phenotype, Biomarkers, Chest computed tomography scan

## Background

Acute respiratory distress syndrome (ARDS) presents with a wide range of clinical and pathological characteristics [1, 2]. Mechanical ventilation is not a single disease-targeted therapy. Moreover, population-based data do not necessarily reflect individual patients with different phenotypes and co-morbidities [3, 4]. The development of treatments and strategies to manage patients with ARDS is complicated by its vast heterogeneity; thus, ARDS mortality remains high [5]. The present review discussed the rationale for personalized mechanical ventilation in ARDS, different ventilatory targets, the role of lung imaging, phenotype identification, physiologically based individualized approaches to ventilation, and a future research agenda. Figure 1 summarises the key points of this review.

### Rationale for personalized mechanical ventilation in ARDS

For clinicians, there is an understandable desire to standardize ventilatory management for patients with ARDS. Results from randomized clinical trials (RCTs)

*Correspondence: ppelosi@hotmail.com
[2] Department of Surgical Sciences and Integrated Diagnostic (DISC), University of Genoa, Viale Benedetto XV 16, Genoa, Italy
Full list of author information is available at the end of the article

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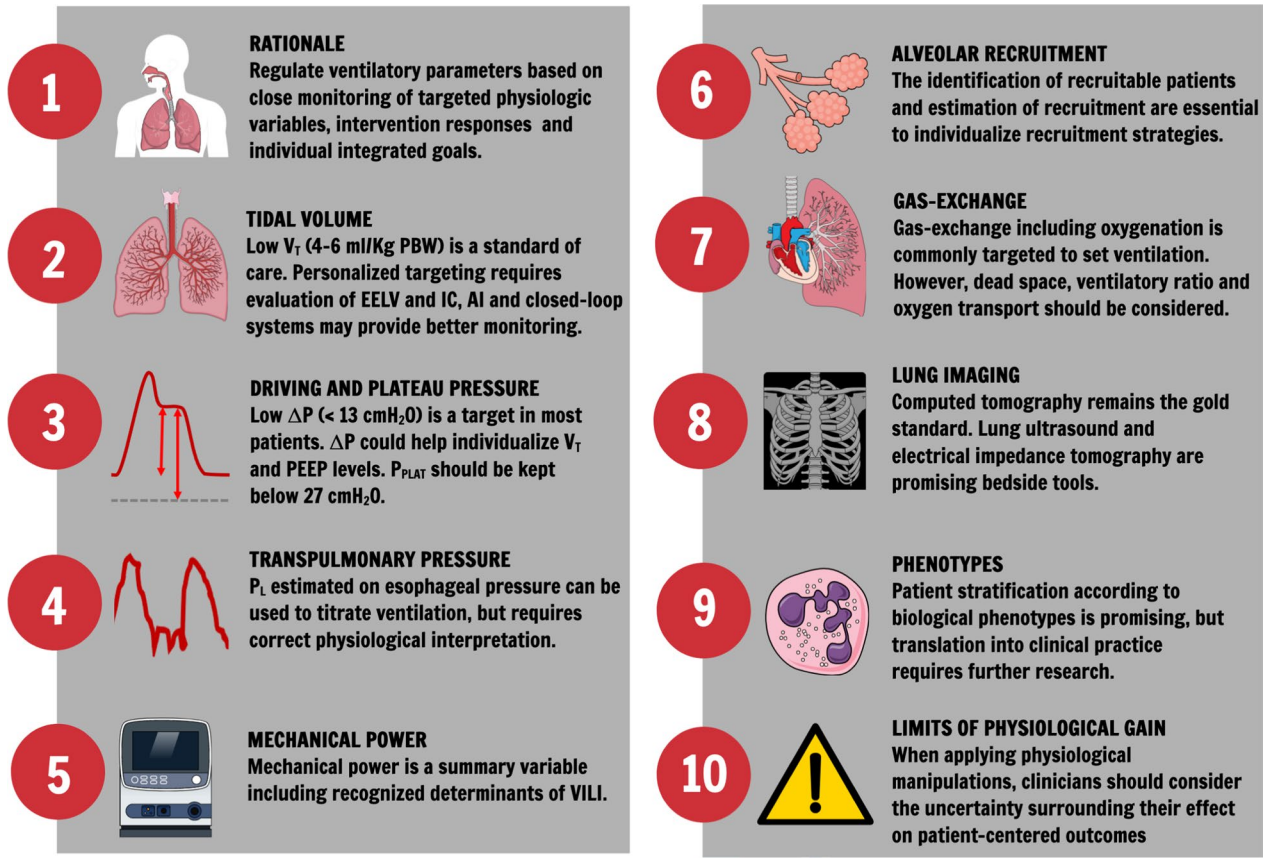
1
RATIONALE
Regulate ventilatory parameters based on close monitoring of targeted physiologic variables, intervention responses and individual integrated goals.
2
TIDAL VOLUME
Low $V_T$ (4-6 ml/Kg PBW) is a standard of care. Personalized targeting requires evaluation of EELV and IC, AI and closed-loop systems may provide better monitoring.
3
DRIVING AND PLATEAU PRESSURE
Low ΔP (< 13 $cmH_2O$) is a target in most patients. ΔP could help individualize $V_T$ and PEEP levels. $P_{PLAT}$ should be kept below 27 $cmH_2O$.
4
TRANSPULMONARY PRESSURE
$P_L$ estimated on esophageal pressure can be used to titrate ventilation, but requires correct physiological interpretation.
5
MECHANICAL POWER
Mechanical power is a summary variable including recognized determinants of VILI.
6
ALVEOLAR RECRUITMENT
The identification of recruitable patients and estimation of recruitment are essential to individualize recruitment strategies.
7
GAS-EXCHANGE
Gas-exchange including oxygenation is commonly targeted to set ventilation. However, dead space, ventilatory ratio and oxygen transport should be considered.
8
LUNG IMAGING
Computed tomography remains the gold standard. Lung ultrasound and electrical impedance tomography are promising bedside tools.
9
PHENOTYPES
Patient stratification according to biological phenotypes is promising, but translation into clinical practice requires further research.
10
LIMITS OF PHYSIOLOGICAL GAIN
When applying physiological manipulations, clinicians should consider the uncertainty surrounding their effect on patient-centered outcomes

**Fig. 1** Summary of recommendations. $V_T$: tidal volume; Δ*P*: driving pressure; PEEP: positive end-expiratory pressure; EELV: end-expiratory lung volume; IC: inspiratory capacity; AI: artificial intelligence; $P_{PLAT}$: plateau pressure; VILI: ventilator-induced lung injury

of interventions and strategies have been combined into meta-analyses to provide summary estimates of treatment effect to inform clinical practice and provide a starting point for a safe individualized approaches to mechanical ventilation [6]. Outcome studies that set thresholds for ventilatory variables based on mortality risk have not established a definitive causal link between the applied pattern, ventilator-induced lung injury (VILI), or death. At the bedside, clinicians seek to implement this evidence and adjust this "powerful instrument" by understanding physiologic mechanisms and possible consequences of ventilatory interventions [7]. Key goals are to relieve excessive workload of breathing and improve gas exchange, without impairing hemodynamics or incurring iatrogenic injury from intolerable pressures or inspired oxygen [8]. Notwithstanding, selective targeting of one of these objectives may collide with goals of another [9]. While using inflexible numerical ventilatory targets throughout all phases of ARDS is nonsensical, tailored ventilation based on careful functional monitoring and mechanistic understanding seems to be both more desirable and justified. Therefore, personalized mechanical ventilation based on lung physiology and response has laid the foundation to develop and inform "smarter" ventilation practices.

*Suggestion 1* Regulate the components of the ventilatory prescription based on close monitoring of targeted physiologic variables, intervention responses, and trends relevant to the integrated goals of treatment for the individual patient.

### Targeting tidal volume

Lung protective ventilation [targeting tidal volume ($V_T$) of 4–6 mL/kg predicted body weight (PBW) to keep plateau pressure ($P_{PLAT}$) below 30 $cmH_2O$] is the current standard of care [10]. In healthy lungs, $V_T$ can be titrated to PBW, since lung volumes are correlated with the PBW. By contrast in ARDS patients, lung volumes do not correlate closely with PBW due to heterogeneous distribution of lung disease. Thus, $V_T$ should ideally be set according to end-expiratory lung volume (EELV) or inspiratory capacity (IC) measured at 30 $cmH_2O$. At higher PEEP, EELV may change with respiratory system compliance

($C_{RS}$), and setting of $V_T$ according to EELV is not reliable. Higher PEEP may not affect or even reduce IC, thus limiting further increases in $V_T$. At lower PEEP, IC correlates more closely with EELV, and $V_T$ may be set by either IC or EELV [11]. Nevertheless, IC is easier for clinicians to measure at bedside compared to EELV [12]. The relationship between $V_T$ and mortality is stronger in patients with lower $C_{RS}$, suggesting the importance of targeting $V_T$ in each patient according to the amount of aeration [3]. Processors within ventilators may automatically calculate the best $V_T$, within safety ranges. For example, adaptive support ventilation, an automated closed-loop mode of ventilation, provides the best combination of $V_T$ and respiratory rate (RR), to achieve the lowest work of breathing combined with the lowest driving pressure ($\Delta P$) and may outperform healthcare professionals with respect to $V_T$ titration [13]. Finally, the use of artificial intelligence to develop a personalized clinical decision support tool could provide needed support to bedside clinicians [14].

*Suggestion 2* Low $V_T$ (4–6 ml/kg PBW) has become a standard of care. The personalized targeting of $V_T$ may necessitate the evaluation of EELV or IC. Automated systems and artificial intelligence may enable better selection, monitoring, and control of optimal $V_T$.

#### Targeting driving and plateau pressure

Driving pressure ($\Delta P = V_T/C_{RS}$) estimates $V_T$ adjusted to functional lung size and has been associated with mortality [15]. Recent studies suggest the importance of using $\Delta P$ to titrate $V_T$ and/or PEEP in ARDS patients [16]. Assuming similar $C_{RS}$, $\Delta P$ is directly correlated with $V_T$. At low $C_{RS}$, a reduced $V_T$ is required to maintain $\Delta P$ within a safe range (< 13 $cmH_2O$). Driving pressure may also be used to set PEEP since the best compromise between overinflation and recruitment is determined at the lowest $\Delta P$ [17]. A study analyzing two randomized ARDS trials found that a decrease in $\Delta P$ was associated with lower mortality compared to increased $Pa_{O2}/FI_{O2}$ [18]. Several concerns exist regarding PEEP titration according to $\Delta P$ including (1) depending on the $V_T$ used, the lowest $\Delta P$ may be achieved at different PEEP levels, (2) at higher $C_{RS}$, compared to lower $C_{RS}$, higher PEEP levels may achieve a lower $\Delta P$, (3) the decrease in $\Delta P$ with PEEP may be associated with greater intratidal recruitment, (4) changes in chest wall compliance may affect the $\Delta P$ measurement, and (5) the presence of airway closure may confound the relationship between $\Delta P$ and PEEP. Although a causal effect has not been demonstrated, $P_{PLAT} > 29$ $cmH_2O$ and $\Delta P > 19$ $cmH_2O$ in moderate/severe ARDS patients have been associated with increased hospital mortality, irrespective of the PEEP and $V_T$ utilized [19]. Specific numerical values, however, may not apply to or be relevant for individual patients [20]. Additionally, the concept of transpulmonary $\Delta P$ during tidal ventilation has been gaining relevance recently and appears to hold potential for better guidance of protective mechanical ventilation.

*Suggestion 3* For most patients, $\Delta P$ should be targeted below 13 $cmH_2O$. Although $\Delta P$ may help "individualize" $V_T$ and PEEP settings, it is not clear whether $\Delta P$ is superior to other methods to set PEEP. Whenever possible, clinicians should aim to keep $P_{PLAT} < 27$ $cmH_2O$.

#### Targeting transpulmonary pressure

Transpulmonary pressure (PL), the distending force of the lung, is the difference between airway ($P_{AW}$) and pleural pressure ($P_{PL}$), with $P_{PL}$ estimated by esophageal pressure ($P_{ES}$) [21, 22]. During controlled mechanical ventilation, $P_{PL}$ varies from non-dependent to dependent lung regions of the lung [23]. The absolute $P_L$ gradient in the supine position primarily depends on lung weight as well as shape and mechanical properties of lung and chest wall. $P_{ES}$ is a reasonable estimate of $P_{PL}$ in the zone between the non-dependent and dependent lung regions. In ARDS, the superimposed pressure from non-dependent to dependent lung regions is 10 $cmH_2O$, on average [24]; thus, $P_{PL}$ is roughly $P_{ES} + 5$ $cmH_2O$ in dependent lung regions and $P_{ES}$-5 $cmH_2O$ in non-dependent lung regions. When interpreting $P_L$ from $P_{ES}$ measurements, the absolute difference (not corrected) between $P_{AW}$ and $P_{ES}$ at end-inspiration or end-expiration represents the $P_L$ in the middle lung, and the difference between end-inspiration and end-expiration in $P_{PL}$ ($\Delta P_{PL}$) approximates $\Delta P_{ES}$. Elastance of respiratory system and chest wall may vary unpredictably and with changes in PEEP. In obese patients or those with increased intraabdominal pressure ($P_{PLAT}$ above 27 $cmH_2O$), a simplified formula may help estimate the required correction of $P_{PLAT}$: $P_{PLAT}$ target + (intraabdominal pressure-13 $cmH_2O$)/2 [25, 26]. In mechanically ventilated non-obese patients, the average intraabdominal pressure is 13 $cmH_2O$ and half of intraabdominal pressure is transmitted to the thoracic cavity [27]. The following parameters have been suggested as potential targets for individualized mechanical ventilation when using $P_L$ [28, 29]: (1) end-inspiratory $P_L$ (non-dependent lung) below 15–20 $cmH_2O$; (2) $\Delta P_L$ below 10–15 $cmH_2O$; (3) PEEP set at end-expiratory $P_L$ (dependent lung) equal to 0–6 $cmH_2O$; and (4) $P_L$ during recruitment maneuvers not to exceed 25 $cmH_2O$ [29, 30]. To date, RCTs evaluating the role of individualized PEEP set according to $P_L$ at end-expiration and compared with low or high $Pa_{O2}/$

$FI_{O2}$ table have not shown beneficial effects on outcomes [31, 32].

*Suggestion 4* In patients with increased intraabdominal pressure or morbid obesity, $P_{L,}$ may assist with individualizing ventilatory settings. The measurement of $P_{ES}$ requires technical skills and physiologic interpretation to be applied by bedside clinicians.

#### Targeting mechanical power

Mechanical power is defined as the amount of energy per unit of time and may vary within the span of an individual inflation or deflation half cycles by alteration in the flow profile [33]. The mechanical power computation is based on the following two equations of motion [34]:

$$\text{PRS} = E_{\text{RS}} \cdot VT + \dot{V} \cdot R_{\text{aw}} \quad (1)$$

$$\text{PRS} = E_{\text{RS}} \cdot VT + \dot{V} \cdot R_{\text{aw}} + \text{PEEP} \quad (2)$$

where $P_{RS}$ is the change in respiratory system pressure, $\dot{V}$ is the inspiratory flow and $R_{\text{aw}}$ the airway resistance. Equation 1 computes the *changes of pressure* from an undefined starting pressure, defining the *change* of the energy level stored in the respiratory system. Equation 2, defines the "absolute" energy level in the respiratory system with reference to its resting state. Multiplying the equations of motion by volume allows the computation of mechanical power for which several formulas are available [35–37].

A strong debate has ensued regarding PEEP and whether associated PEEP volume must be considered [38, 39] in the computation of mechanical power. Does adding a $\Delta P$ of 1 cm $H_2O$ to an already inflated lung (40 $cmH_2O$ of PEEP) produce a similar lung injury as when the same $\Delta P$ starts from 0 cm $H_2O$ PEEP? Supporters of the first equation of motion suggest that what really counts is the change. They claim that the energy required to climb one step on a staircase is the same regardless of which step one is starting from, as though the "rising the steps" occurs in a constant force field. In contrast, supporters of the second equation of motion claim that the force field varies with lung inflation. By analogy, it is as if a person climbed the stairs with an elastic band around the waist somehow anchored to the first step. Each step therefore requires more energy, and more energy results in more strain, and more strain results in more VILI. At present, there is a lack of agreement on the computation underpinning the calculation of mechanical power and determinants (PEEP levels, frequency, and lung size) that should be taken into consideration, and therefore, personalization is not possible. Although readily measured at the bedside, its value in VILI prediction remains controversial [40–42].

*Suggestion 5* Mechanical power is a summary construct that includes all of the important and well-recognized determinants of VILI. The same mechanical power value can be reached with different combinations of the above variables.

#### Targeting alveolar recruitment

Ventilation strategies that target alveolar recruitment are based on the premise that a significant proportion of the volume loss within the ARDS "baby lung" [43] is due to alveolar edema and/or collapse, potentially be "recruited" to participate in gas exchange [44]. Recruitment maneuvers (RMs) typically apply higher airway pressures to open previously collapsed regions of lung. Higher PEEP levels are subsequently used to keep recruited alveoli open throughout the ventilation cycle. The safety of ventilation strategies targeting lung recruitment has been questioned. The ART trial [45] demonstrated that high-pressure stepwise lung recruitment maneuvers (to $P_{\text{PLAT}} = 50–60$ $cmH_2O$) combined with higher PEEP titration increased patient mortality [45]. In contrast, the PHARLAP trial [46] tested a less aggressive recruitment strategy ($P_{\text{PLAT}} \leq 28$ $cmH_2O$), but was stopped early as the intervention group experienced higher rates of new cardiac dysrhythmias. A recent meta-analysis showed that at low $V_T$, the routine use of higher PEEP and/or RMs did not reduce mortality among unselected ARDS patients [47]. In ARDS patients with a significant amount of collapsed lung, recruitment of these units could potentially reduce the pressure needed to accommodate a given $V_T$ and the energy transmitted to individual lung units. Conversely, if these approaches do not recruit significantly collapsed alveoli, then the increased airway pressures could cause overdistension of open lung with negative cardiovascular effects. Monitoring the response to lung recruitment maneuvers at the bedside, regarding their effect on apparent lung compliance, is critical. A bedside approach to estimate recruitability has recently been proposed by abruptly releasing PEEP (from 15 to 5 $cmH_2O$) with an increase in expired volume [48]. Briefly, the difference between expired volume and the volume predicted by compliance at low PEEP (or above airway opening pressure) estimates the recruited volume by PEEP. This recruited volume divided by the effective pressure change estimates the compliance of the recruited lung; the ratio of the compliance of the recruited lung to the compliance at low PEEP measures the recruitment-to-inflation ratio. The recruitment-to-inflation ratio may help to identify ARDS patients who are recruitable at the bedside.

*Suggestion 6* The identification of recruitability in ARDS patients, such as by the estimation of alveolar recruitment at bedside, is essential to personalize the use of recruitment strategies. However, systematic use of RMs is not associated with better outcome.

### Targeting gas exchange

The use the $PaO_2/FiO_2$-PEEP table has become a standard by which clinicians set PEEP. The largest trial investigating the effects of different ventilatory strategies in ARDS used a $PaO_2/FiO_2$-PEEP table to set PEEP. However, $PaO_2/FiO_2$ depends on $FiO_2$ and PEEP levels affect cardiac output (CO). Recently, the concept of "keeping the lung at rest with permissive atelectasis and minimal oxygenation targets" has been proposed [49]. Oxygen consumption ($VO_2$) is dependent on oxygen delivery ($DO_2$); consequently, maximizing $DO_2$ might be considered an alternative therapeutic goal for managing ARDS patients [50, 51]. Both a meta-analysis [52] and RCTs [53, 54] have failed to show benefits on outcomes from maximizing $DO_2$. In ARDS patients, it is important to individually maintain an adequate $DO_2$ and hence adequate CO as opposed to targeting supra-normal values of $DO_2$. Central venous oxygen saturation ($ScvO_2$), as a reflection of the $VO_2/DO_2$ balance, may be a good marker of CO adequacy [55]. However, ARDS associated with sepsis or marked systemic inflammation impairs oxygen extraction capabilities and renders $ScvO_2$ uninterpretable [56]. In these conditions, the difference between central venous and arterial $CO_2$ pressure ($PCO_2$ gap) is useful since it is not affected by altered oxygen extraction. A $PCO_2$ gap higher than 6 mmHg is indicative of inadequate $DO_2$ and is increased in the presence of shock. Physiologic dead space is the portion of each $V_T$ that does not take part in gas exchange and represents a good "global index" of the efficiency of the lung function being strongly associated with outcome and helpful for PEEP setting [57, 58]. However, dead space is not routinely measured in critical care practice, because of the difficulties in interpreting capnograms and the different calculation methods. The ventilation ratio and $P_{ET}CO_2/PaCO_2$ ratio, though less precise, appear to be an excellent surrogate for physiologic dead space [59, 60].

*Suggestion 7* Gas exchange, including oxygenation, is a widely used parameter to set mechanical ventilation in ARDS. Physiologic dead space and the ventilation ratio should be also considered, taking into account *the balance* between aeration and perfusion. The measurement of $PCO_2$ gap is important to individually identify inadequate $DO_2$.

### Targeting lung imaging

Different imaging techniques have been proposed to personalize mechanical ventilation strategies. Lung ultrasound (LUS) and electric impedance tomography (EIT) may be performed at bedside, while chest computed tomography (CT) scan require transportation of patients outside of the intensive care unit (ICU). Chest CT scan allows the detection of relevant parenchymal alterations including the amount and regional lung distribution of hyperinflated, aerated, and non-aerated lung tissue [61]. Two main chest CT phenotypes have been proposed [62]: (1) lobar attenuations (e.g., focal findings) associated with minimal loss of lung volume, less increase in lung weight, a linear pressure–volume curve of the respiratory system, with minimal alveolar recruitment and increased hyperinflation in response to increased PEEP, and (2) diffuse or patchy attenuations (e.g., non-focal findings) associated with major loss of lung volume, marked increases in lung weight, a curvilinear pressure–volume curve of the respiratory system, with greater alveolar recruitment and less hyperinflation in response to an increase in PEEP. Recruitment maneuvers yield less hyperinflation in patients with non-focal compared to focal chest CT morphology [63]. Chest CT morphology, in turn, may be associated with different biomarkers [64] and impaired alveolar clearance [5]. A recent clinical trial [65] found no differences in outcome between standard lung–protective ventilation and personalized ventilation based on the morphology of consolidations, the "open–lung strategy" consisting of high PEEP with RMs and rescue prone positioning in patients with non-focal ARDS while low PEEP without RMs and early prone positioning in focal ARDS. Patients that were misclassified in the personalized ventilation group had higher mortality compared to patients that received the intended ventilation strategy.

Dual-energy CT scan has been recently used to investigate ventilation perfusion relationships at different ventilation settings in COVID-19 patients [66]. LUS has been proposed as an alternative tool to monitor lung morphology at bedside [67], for several reasons: (1) LUS and chest CT findings are well correlated with regard to aeration [68] and identifying patients with focal or non-focal ARDS morphology [69], (2) LUS may influence clinical decision making related to the individualized mechanical ventilation management [70, 71], and (3) worsening aeration in several LUS regions, associated with deterioration of respiratory mechanics and blood gases, requires prompt reevaluation of mechanical ventilation settings. Notwithstanding, sensitivity of LUS to detect alveolar recruitment is variable across studies [68]. Conversely, EIT assesses regional differences between inspiratory and expiratory aeration and permits in-depth characterization of ARDS phenotypes at the bedside [72]. PEEP, when

set according to EIT, may aid in optimizing lung recruitment and homogeneity of ventilation [73]. Technological development by EIT may also quantitatively estimate regional lung perfusion based on first-pass kinetics of a bolus of hypertonic saline contrast [74, 75]. To evaluate lung morphology and the potential for recruitment, ARDS patients should ideally undergo chest or lung imaging at different pressures.

*Suggestion 8* Imaging techniques may help to better identify different lung morphology and response to ventilation strategies. Chest CT allows detailed and quantitative analysis of overdistended lung: normally aerated, poorly aerated and non-aerated tissue, as well as consolidated and atelectatic components. LUS and EIT are promising tools for clinicians to use at the bedside.

#### Targeting biological phenotypes

ARDS is characterized by different pathogenetic pathways leading to similar clinical presentations postulated to represent distinct phenotypes, which may enable precision therapy. To date, two different ARDS phenotypes (hyperinflammatory and hypoinflammatory) have been identified that differ in response to therapy and outcomes. Post hoc latent class analysis of a panel of blood biomarkers for inflammation, endothelial injury, and coagulopathy combined with clinical variables has revealed two phenotypes in 5 RCTs [76–80]. Similarly, post hoc cluster analysis of a set of biomarkers for inflammation, endothelial injury and coagulopathy without clinical variables also revealed two phenotypes in an observational study [81]. Of interest, the phenotypes had a differential or even opposite response to PEEP, fluid management, and simvastatin treatment [76–78, 80]. Recently, point-of-care breath testing introduced the possibility for targeted exhaled breath analysis to be used as a bedside test and potentially a diagnostic tool for timely ARDS detection [82]. Genome-wide association studies sequencing of hundreds-of-thousands to millions of DNA variants (single nucleotide polymorphisms) may help to identify individual patients who display a phenotype or trait that may be more or less amenable to a specific treatments [83]. The personalized approach to treatment based on identification of phenotypes according to different biomarkers is based on two main assumptions: (1) the patient's phenotype can be correctly identified and (2) treatment needs to be individually targeted and effective for specific phenotypes. However, the personalized approach to treatment based on phenotypes may be associated with better outcomes in diseases with a single identifiable factor or etiology, such as cancer. Conversely, in ARDS, the disease etiology and progression may be linked to multiple factors. Thus, the efficacy of a specific treatment is not assured even if individual phenotypes are identified correctly. Care must be taken to refrain from prematurely positive interpretations of secondary analyses of previously collected data, which have not been validated in prospective cohorts or RCTs. To date, no mechanical ventilation guidelines have included statements regarding different ARDS phenotypes.

*Suggestion 9* The stratification of ARDS patients according to different phenotypes is promising but awaits clinical confirmation before it can be translated into to the clinical setting.

#### The seduction of short-term physiological gains

In daily practice, critical care physicians use physiological data to aid them in guiding and adjusting therapies. However, clinicians are not able to accurately predict the medium- or long-term consequences of physiologically based therapy on patient-centered outcomes. Clinicians often fall prey to celebrating immediate physiological gains under the pretense that they will translate into improvements in desired outcomes. In this regard, physiological gains can be seductive. When these gains are achieved, clinicians feel validated (immediacy bias) regardless of the downstream future effects which are unknown. When anticipated gains are not achieved, clinicians engage in attribution bias-blaming severe and unresponsive illness. Short-term physiological gains are an elusive concept. For example, in an ARDS patient on PEEP = 8 $cmH_2O$ and $FiO_2 = 0.6$ to maintain a $PaO_2 = 60$ mmHg, increasing PEEP to 14 $cmH_2O$ may achieve the same $PaO_2$ at an $FiO_2 = 0.5$. Some clinicians may see that as physiological success. However, apportioning "value" to this increase in PEEP prioritizes lung mechanics and lung physiology because they can be measured. However, the impact of the increased PEEP on renal function, gastrointestinal permeability, or the brain typically remains unmeasured and unknown. This is a fundamental problem with physiology: it measures whether a specific intervention affects a specific set of physiological parameters. However, it does not assess "other" unmeasured or unintended physiological consequences. Thus, physiologically based personalized therapy, although clearly important at the extremes of illness, become problematic at intermediate levels of illness where safety has typically been established. Historically, the pursuit of perceived physiological success in the belief that it would lead to subsequent clinical success has often proved to be disappointing with notable examples including intensive insulin therapy to normalize glycemia [84]; drotrecogin alpha to normalize activated protein C levels [85]; colloid resuscitation to increase intravascular volume [86]; decompressive craniectomy to lower intracranial pressure in diffuse cerebral injury [87]; hypothermia

for out of hospital cardiac arrest [88], early parenteral or enteral nutrition to achieve early full caloric intake [89]; glutamine therapy to correct glutamine deficiency [90]; fluid bolus resuscitation in septic African children [91]. All this does not imply that physiology should not be used to guide therapies in patients with ARDS. However, clinicians should be aware that improvement in physiological variables during individualized targeted therapy does not necessarily imply clinical safety or improved outcomes.

*Suggestion 10* When applying physiological manipulations, clinicians should consider the uncertainty surrounding their subsequent effect on patient-centered outcomes.

### Future research agenda

Personalized mechanical ventilation in ARDS merits further research on specific targets: (1) characterize biomarkers profiles and responses to specific treatments associated with pulmonary or extrapulmonary insults, pulmonary inflammation, and lung physiology; (2) the use of mechanical power and $P_L$; and (3) identification of patient's phenotype according to the biomarkers of epithelial and endothelial cell damage, inflammation, and extracellular matrix. The investment of personalized mechanical ventilation is high and will require investment of both personnel and resources, including experimental and clinical trials.

## Conclusions

A personalized mechanical ventilation approach based on lung physiology and morphology, ARDS etiology, lung imaging as well as identification of biological phenotypes may improve and individualize future mechanical ventilation practice. Additional research is warranted before personalized mechanical ventilation strategies can be applied at the bedside of ARDS patients.

#### Abbreviations

ARDS: Acute respiratory distress syndrome; RCT: Randomized clinical trial; VILI: Ventilator induced lung injury; $V_T$: Tidal volume; PBW: Predicted body weight; $P_{PLAT}$: Plateau pressure heterogeneous distribution of lung disease; EELV: End-expiratory lung volume; IC: Inspiratory capacity; PEEP: Positive end-expiratory pressure; $C_{RS}$: Respiratory system compliance; RR: Respiratory rate; $\Delta P$: Driving pressure; PL: Transpulmonary pressure; $P_{AW}$: Airway pressure; $P_{PL}$: Pleural pressure; $P_{ES}$: Esophageal pressure regions; $\Delta P_L$: Transpulmonary driving pressure; $P_{RS}$: Respiratory system pressure; $\dot{V}$: Inspiratory flow; $R_{aw}$: Airway resistance; RM: Recruitment maneuver; $FiO_2$: Inspired oxygen fraction; CO: Cardiac output; $VO_2$: Oxygen consumption; $DO_2$: Oxygen delivery; $ScvO_2$: Central venous oxygen saturation; $PCO_2$ gap: Central venous and arterial $CO_2$ pressure difference; $P_{ET}CO_2$: End-tidal $CO_2$; LUS: Lung ultrasound; EIT: Electric impedance tomography; CT: Computed Tomography; ICU: Intensive care unit.

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PP and PRMR designed this review. All authors contributed equally to literature revision and manuscript writing. All authors revised and approved the final version of the manuscript.

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#### Consent for publication

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#### Author details

[1]Anesthesia and Intensive Care, San Martino Policlinico Hospital, IRCCS for Oncology and Neuroscience, Genoa, Italy. [2]Department of Surgical Sciences and Integrated Diagnostic (DISC), University of Genoa, Viale Benedetto XV 16, Genoa, Italy. [3]Pneumology and Intensive Care Medicine, University of São Paulo, São Paulo, Brazil. [4]Adult Intensive Care Unit, Albert Einstein Hospital, São Paulo, Brazil. [5]Department of Intensive Care, Austin Hospital, Melbourne, VIC, Australia. [6]Department of Epidemiology and Preventive Medicine, Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne, VIC, Australia. [7]Data Analytics Research and Evaluation Centre, The University of Melbourne and Austin Hospital, Melbourne, Australia. [8]Department of Intensive Care, Royal Melbourne Hospital, Melbourne, VIC, Australia. [9]Department of Critical Care, The University of Melbourne, Melbourne, Australia. [10]Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, ON, Canada. [11]Unity Health Toronto-St. Michael's Hospital, Li Ka Shing Knowledge Institute, Toronto, ON, Canada. [12]Intensive Care Unit of the Shaare Zedek Medical Medical Centre, Hebrew University Faculty of Medicine, Jerusalem, Israel. [13]Department of Anaesthesiology, Emergency, and Intensive Care Medicine, University of Göttingen, Göttingen, Germany. [14]Anaesthesia and Intensive Care Medicine, University Hospital Galway, and School of Medicine, National University of Ireland, Galway, Ireland. [15]University of Minnesota and Regions Hospital, St. Paul, MN, USA. [16]Department of Anaesthesiology, Critical Care and Pain, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, India. [17]Mahidol Oxford Tropical Medicine Research Unit (MORU), Mahidol University, Bangkok, Thailand. [18]Service de Médecine Intensive-Réanimation, Hôpital Bicêtre, Inserm UMR S_999, AP-HP Université Paris-Saclay, Le Kremlin-Bicêtre, France. [19]Laboratory of Pulmonary Investigation, Carlos Chagas Filho Institute of Biophysics, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil. [20]Department of Intensive Care, Amsterdam University Medical Centers, Amsterdam, The Netherlands. [21]Nuffield Department of Medicine, University of Oxford, Oxford, UK.

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